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Upper gastrointestinal bleeding as the initial manifestation of gastroenteropancreatic neuroendocrine tumors

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ABSTRACT

A 78-year-old man presented with upper gastrointestinal bleeding, which was biopsy proven to be from a gastric neuroendocrine tumor. By the time of diagnosis, he developed liver metastasis and died 2 months later. Upper gastrointestinal bleeding is an uncommon feature in gastroenteropancreatic neuroendocrine tumor.

KEYWORDS Gastroenteropancreatic neuroendocrine tumor; hematemesis; upper gastrointestinal bleeding

Gastrointestinal (GI) tumor bleeding accounts for 4.5% of all severe upper GI bleeding cases.[1] Upper GI bleeding leads to the first diagnosis of cancer in half of these patients; the other half have a known prior cancer.[1] Gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are rare neoplasms originating from neuroendocrine cells of the GI tract. The clinical symptoms are based on the tumor's ability to produce hormone, as well as anatomical location, mass effects, and distant metastases.[2] It is rare for GEP-NETs to present with upper GI bleeding. We report a case of metastatic gastric NET presenting with upper GI bleeding as the first symptom of GEP-NET.

CASE PRESENTATION

A 78-year-old man with hypertension, persistent atrial fibrillation, coronary artery disease with previous coronary artery bypass grafting, history of implantable cardioverter defibrillator placement, and mitral stenosis with previous bioprosthetic mitral valve replacement presented to the emergency department with dark tarry stool for 1 day. His home medications included apixaban for a recent valve replacement, pantoprazole, diltiazem, spironolactone, rosuvastatin, dofetilide, metoprolol, and tamsulosin. He also had an unintentional weight loss of 15 lbs in 1 month due to poor appetite. He was nonalcoholic with no past history of cirrhosis or peptic ulcer disease. He was hypotensive with a blood pressure of 80/40 mm Hg. The physical examination was unremarkable. His initial laboratory results were remarkable for a hemoglobin of 10 g/dL, platelet count of 344 k/μL, prothrombin time of 20.6 seconds, international normalized ratio of 1.8, blood urea nitrogen of 82 mg/dL, creatinine of 3.9 mg/dL, aspartate aminotransferase of 43 IU/L, alanine aminotransferase of 43 IU/L, alkaline phosphatase of 890 IU/L, and gamma-glutamyl transferase of 838 IU/L.

Abdominal ultrasonography showed gallbladder distention and an enlarged liver with diffuse infiltration with numerous low-density echogenic masses suggestive of metastasis *(Figure 1a)*. Esophagogastroduodenoscopy revealed a normal esophagus and a large fungating infiltrative ulcerated mass involving the gastric antrum and pylorus *(Figure 1b)*. Gastric body biopsy showed mild chronic gastritis. Histopathologic evaluation of the gastric mass showed a grade 3 well-differentiated NET. The tumor cells were positive for synaptophysin, CD56, and pancytokeratin with very rare cells weakly positive for CDX2 *(Figure 2)* while negative for CK7 and CK20. Ki67 staining showed a high proliferative index of 90% with 24 mitoses per 2 mm^2. Ultrasound-guided core needle biopsy of the liver mass revealed the same type of NET on histopathology. Further staging of the cancer with contrast computed tomography was postponed due to his concomitant acute kidney injury.

Four weeks later, the patient developed anemia from ongoing upper GI bleeding from gastric mass, *Streptococcus oralis mitis* bacteremia, and worsening jaundice from liver metastasis. He underwent another esophagogastroduodenoscopy and

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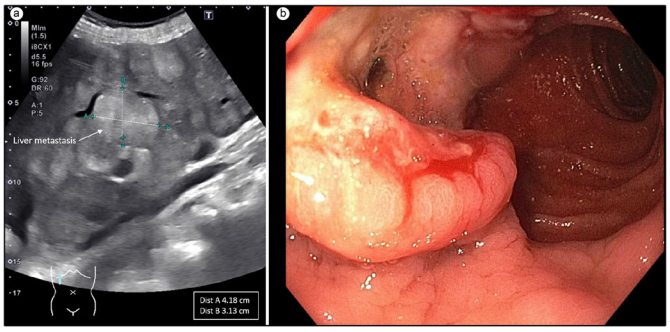

Figure 1. **(a)** Abdominal ultrasonography showing gallbladder distention and an enlarged liver with diffuse infiltration with numerous low-density echogenic mass suggestive of metastasis. **(b)** Esophagogastroduodenoscopy revealing a normal esophagus and a large fungating infiltrative ulcerated mass involving the gastric antrum and pylorus.

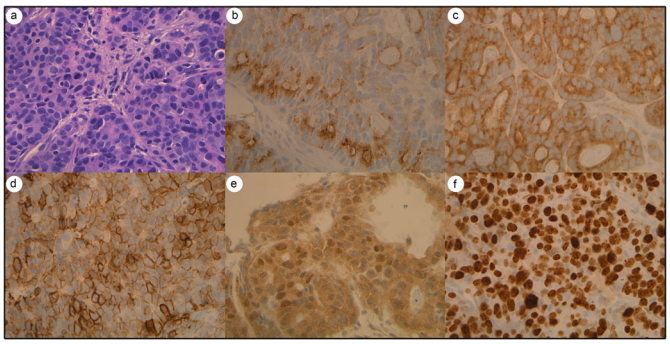

Figure 2. Grade 3 well-differentiated gastric neuroendocrine tumor. **(a)** Hematoxylin and eosin staining; **(b)** positive chromogranin A staining; **(c)** positive synaptophysin staining; **(d)** positive CD56 staining; **(e)** weakly positive CDX-2 staining; and **(f)** Ki-67 proliferation index of 90%.

had hemostatic spray applied to the ulcerated mass with oozing and stigmata of recent bleeding. He was discharged home after 5 days of hospitalization. He died 2 months after the diagnosis.

DISCUSSION

Our patient presented with upper GI bleeding from a well-differentiated gastric NET that was classified as grade 3 due to the high proliferation index determined by Ki-67 and mitotic rate on histopathologic examination. The patient had liver metastases at the time of diagnosis and died 2 months later. Well-differentiated NETs display a spectrum of aggressiveness, with the prognosis and survival inversely related to the Ki-67 index and mitotic rate.[3] Liver is the predominant site of metastatic well-differentiated NETs.

Upper GI bleeding can be the initial manifestation of the primary or metastatic GI malignancy.[4] Endoscopic findings of a friable ulcerated mass or irregular ulcer margins are suspicious for malignancy and indicate the need for biopsy. GI-related tumor bleeding is challenging for endoscopic hemostasis due to multiple factors, such as vascular invasion and neovascularization of the tumors and cancer-related coagulopathy, resulting in high rates of rebleeding.[5,6] Current endoscopic treatments for GI-related tumor bleeding are injection therapy with epinephrine or ethanol, thermal therapy, radiofrequency ablation, endoloops, argon plasma coagulation, and hemostatic powder. Patients with upper GI bleeding secondary to GI malignancy have a low survival, as most die within 1 year.[6]

GEP-NETs have been rarely implicated in upper GI bleeding, accounting for only 0.18% in one study,[6] including NETs of pancreatic,[7–9] gastric,[10] and small intestine origin.[11] Gastric and ileal NETs have led to massive hematemesis and melena, respectively. Pancreatic NETs have contributed to upper GI bleeding from either gastric metastasis in the form of an ulcerative mass[7] or from gastric varices resulting from local invasion of the splenic vein by the infiltrating tumor.[8,9] Gastric metastases from pancreatic NETs have resulted in large ulcerative masses in the cardia of the stomach infiltrating into the muscularis propria along with diffuse thickening and congestion of gastric folds.[8] Our patient likely developed GI bleeding from an infiltrating ulcerated mass in the gastric antrum and pylorus.

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